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TAIWAN LIPOSOME CO LTD *DE 19913640-A1
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Pharmaceutical composition comprising drug, e.g. anticancer agent, encapsulated in liposomes, containing polymer-lipid conjugate as stabilizer to inhibit liposome aggregation
C2000-192592

Addnl. Data: CHENG J

A(12-V1) B(1-D2, 2-D, 2-M, 4-B1B, 4-B3A, 4-C3C, 5-A3B, 5-B1P, 6-D9, 6-D18, 6-E5, 12-M6, 12-M11F, 14-H1B) .13

NOVELTY

In a pharmaceutical composition including an active agent (A) encapsulated in liposomes, aggregation of the liposomes is inhibited using a polymer-lipid conjugate (I), such that the integrity of the liposomes and the storage stability of the composition are improved.

DETAILED DESCRIPTION

An INDEPENDENT CLAIM is included for the preparation of the compositions.

USE

The liposomes are useful as a dosage form for (A), e.g. for targeted delivery of anticancer agents.

ADVANTAGE

(I) is effective in stabilizing the liposome formulations at sufficiently small amounts to cause no undesirable side effects (such as reduction of anticancer agent accumulation in tumor regions). Typically addition of 0.6 mol. % of a polyalkyl ether lipid derived from polyethylene glycol-5000 to liposomes containing doxorubicin prevents aggregation and precipitation for at least 90 days. In some cases the liposomes may have an effective life of more than 1 year.

EXAMPLE

Distearoyl phosphatidyl choline and cholesterol (molar ratio 3 : 2) were dissolved in chloroform. After mixing and removing the solvent, the residue was rehydrated with 150 mM ammonium sulfate (AS) solution (pH 5.0) at 55 °C. The mixture was subjected to five liquid nitrogen freezing/thawing cycles, extruded five times at below 60 °C using a 0.1 micro m polycabonate membrane and filtered through a 0.05 micro m membrane to give a liposomes containing AS. AS

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outside of the liposomes was removed using Sephadex G-50 (RTM), then 1 mg of doxorubicin per 10 micro mol phospholipid was added. The mixture was heated to 60 °C, stirred at 100 rpm for 30 minutes, flash-cooled with ice for 3 minutes and allowed to warm up. The doxorubicin outside the liposomes was removed on a molecular sieve column, eluting with 0.9 % sodium chloride solution. The liposome-containing fraction was collected, filtered through a 0.22 micro m membrane and gassed with argon to facilitate storage. The obtained liposomes containing doxorubicin were treated with 0.6 mol. % of a polyethylene glycol-5000 derivative of distearoyl phophatidyl choline-ethanolamine. The solutions were stored for 24 hours at 37 °C then at 4 °C. No aggregation or precipitation was observed after 90 days.

TECHNOLOGY FOCUS

Pharmaceuticals - Preferred Components: (I) is a polyalkyl ether lipid. (A) is 1-β-D-arabinofuranosyl-cytosine, arabinoside, cis-diaminochloroplatinum, doxorubicin, daunorubicin, vincristine, vinblastine, navelbine, antifolate, taxol, topotecan, mitomycin C or camptothecin.

Preparation: Claimed preparation of the composition comprises:

(i) encapsulating (A) in liposomes, adding (I) and allowing the mixture to stand;

(ii) preparing liposomes containing (I) and encapsulating (A) in the liposomes; or

(iii) adding (I) to previously prepared liposomes, allowing the mixture to stand and encapsulating (A) in the liposomes.

In all cases (I) is a polyalkyl ether lipid of molecular weight 200 - 2000, and is added at 0.01 - 1 mol. % based on the liposomes.

Polymers - Preferred Materials: (I) is a polyalkyl ether lipid derived from polyethylene glycol, polymethylethylene glycol, polypropylene glycol, polyhydroxypropylene glycol, polymethylpropylene glycol, polyhydroxypropylene oxide or polyethylene/polypropylene glycol. (11pp2400DwgNo.0/3)

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